Decision Summary

CMS on June 4, 2009 opened a reconsideration of Section 220.6 of the National Coverage Determinations Manual to review evidence on the use of NaF-18 (sodium fluoride-18) imaging (NaF-18 PET) to identify bone metastasis of cancer. CMS proposes that the evidence is not sufficient to determine that the results of NaF-18 PET imaging to identify bone metastases improve health outcomes of beneficiaries with cancer. Therefore we propose that this use is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act).

However, CMS proposes that the available evidence is sufficient to determine that NaF-18 PET imaging, to identify bone metastasis of cancer to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment, is reasonable and necessary under §1862(a)(1)(E) through Coverage with Evidence Development (CED).

Therefore, we propose to cover NaF-18 PET imaging when the beneficiary's treating physician determines that the NaF-18 PET study is needed to inform to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment, and when the beneficiary is enrolled in, and the NaF-18 PET provider is participating in, the following type of prospective clinical study:

An NaF-18 PET clinical study that is designed to collect additional information at the time of the scan to assist in initial treatment planning and in identification of symptomatic bone metastases. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The clinical studies for which Medicare will provide coverage must answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the NaF-18 PET study results are needed to to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment, does the addition of NaF-18 PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Act.

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Proposed Decision Memo

TO: Administrative File: CAG #00065R1 Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer

FROM: Tamara Syrek Jensen, JD
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SUBJECT: Proposed Coverage Decision Memorandum for Positron Emission Tomography (NaF-18 PET) to Identify Bone Metastasis of Cancer (CAG-00065R1)

DATE: November 30, 2009

I. Proposed Decision

CMS on June 4, 2009 opened a reconsideration of Section 220.6 of the National Coverage Determinations Manual to review evidence on the use of NaF-18 (sodium fluoride-18) imaging (NaF-18 PET) to identify bone metastasis of cancer. CMS proposes that the evidence is not sufficient to determine that the results of NaF-18 PET imaging to identify bone metastases improve health outcomes of beneficiaries with cancer. Therefore we propose that this use is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act).

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Therefore, we propose to cover NaF-18 PET imaging when the beneficiary's treating physician determines that the NaF-18 PET study is needed to inform to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment, and when the beneficiary is enrolled in, and the NaF-18 PET provider is participating in, the following type of prospective clinical study:

An NaF-18 PET clinical study that is designed to collect additional information at the time of the scan to assist in initial treatment planning and in identification of symptomatic bone metastases. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The clinical studies for which Medicare will provide coverage must answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the NaF-18 PET study results are needed to to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment, does the addition of NaF-18 PET imaging lead to:

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d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
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l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Act.

II. Background

NaF-18 PET
Throughout this memorandum, we use the term NaF-18 to refer to fluorine-18 labeled sodium fluoride, also known as F-18 sodium fluoride. We use the term PET to refer to positron emission tomography or to a positron emission tomogram, depending on context. We include integrated positron emission tomography – computerized tomography (PET/CT) in the term PET. NaF-18 PET refers to PET imaging utilizing NaF-18 as the radioactive tracer. The abbreviation MBq stands for megabecquerel, a unit of radioactivity. The abbreviation mCi denotes millicuries, an alternative unit of radioactivity (1 mCi = 37 MBq). The abbreviation BS refers to either bone scan or bone scintigraphy.

Following initial FDA approval in 1972 under New Drug Application (NDA) 17-042 for clinical imaging studies (as noted in NIH 2008), NaF-18 PET has been recognized as an excellent technique for imaging areas of altered osteogenic activity in bone. NaF-18 has desirable characteristics for this use, including rapid bone uptake, very rapid blood clearance (resulting in a favorable bone-to-background tissue ratio within one hour after NaF-18 intravenous administration), and a reasonable decay half-life (110 minutes). In addition, there is wide availability of tomographic imaging equipment capable of detecting the 0.511 MeV gamma rays produced by electron-positron annihilation following F-18 beta (+) decay (the same gamma ray energy produced by F-18 fluorodeoxyglucose (FDG) PET imaging studies). Some authors also cite advantages of NaF-18 PET in nuclear medicine department workflow and patient convenience compared with those associated with use of ^{99m}Tc (Grant FD et al., 2008).

The clinical value of detecting and assessing the initial extent of metastatic cancer in bone is attested by a number of professional guidelines for oncology. Imaging to detect bone metastases is also recommended when a patient, following completion of initial treatment, is symptomatic with bone pain suspicious for metastases from a known primary tumor.

III. History of Medicare Coverage

All uses of NaF-18 PET are currently nationally non-covered by Medicare. Section 220.6 of the NCD Manual includes the following provision.

I. General Description

Positron emission tomography (PET) is a noninvasive diagnostic imaging procedure that assesses the level of metabolic activity and perfusion in various organ systems of the [human] body. A positron camera (tomograph) is used to produce cross-sectional tomographic images, which are obtained from positron emitting radioactive tracer substances (radiopharmaceuticals) such as 2-[F-18] Fluoro-D-Glucose (FDG), that are administered intravenously to the patient.

The following indications may be covered for PET under certain circumstances. Details of Medicare PET coverage are discussed later in this section. Unless otherwise indicated, the clinical conditions below are covered when PET utilizes FDG as a tracer.

NOTE: This manual section 220.6 lists all Medicare-covered uses of PET scans. Except as set forth below in cancer indications listed as "Coverage with Evidence Development", a particular use of PET scans is not covered unless this manual specifically provides that such use is covered.

A. Current Request

CMS internally generated a request to reconsider the non-coverage of NaF-18 PET for the identification of bone metastasis of cancer.

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. NaF-18 PET falls within the following benefit category: other diagnostic tests §1861(s)(3).

Medicare regulations at 42 C.F.R. § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem."

IV. Timeline of Recent Activities

June 4, 2009	CMS posted a tracking sheet on the website and the initial 30 day public comment period began.

V. Food and Drug Administration (FDA) Status

According to FDA staff, a new drug application (NDA) for NaF-18 has been submitted to FDA.

VI. General Methodological Principles

When making NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for Medicare beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary under § 1862(a)(1)(A) of the Act.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review.

As noted above, with respect to diagnostic tests, the Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of an NaF-18 PET imaging test for cancer metastasis to bone in order to assist in initial treatment planning and in identification of symptomatic bone metastases in the anticancer management of patients who are known to have cancer based on clinical findings and preliminary diagnostic testing.

B. Discussion of evidence reviewed

1. Questions & Outcomes of Interest

1. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully alter the recommended treatment strategy for beneficiaries who have cancer, either for initial treatment planning or for identification of bone metastases in symptomatic patients following treatment for cancer?

2. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully improve patient centered health outcomes for beneficiaries who have cancer, either for initial treatment planning or for identification of bone metastases in symptomatic patients following treatment for cancer?

As a diagnostic test, NaF-18 PET would not be expected to directly change health outcomes, i.e. there is no evidence that the administration of NaF-18 is therapeutic for cancer in and of itself. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available treatment options.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but also include beneficial or adverse clinical effects, such as changes in management due to test findings or preferably, improved health outcomes for Medicare beneficiaries. Ideally, we would see evidence that the systematic incorporation of NaF-18 PET results into treatment decisions leads physicians to prescribe different treatment than they would otherwise have prescribed, and that those patients whose treatment is changed by test results achieve improved outcomes.

2. External technology assessments

CMS did not commission an external TA for this reconsideration. A review of current literature about NaF-18 PET and cancer metastases to bone was performed in March 2009 by the Cancer Imaging Program of the Division of Cancer Treatment and Detection of the National Institutes of Health (NIH). NIH kindly provided copies of this review to CMS. Selected articles about oncologic uses of PET have been separately reviewed by CMS staff and are summarized below, to determine what evidence from clinical trials exists about the impact of NaF-18 PET on either treatment decisions or outcomes for patients with known or suspected metastatic cancer to bone.

Note that in a number of these studies, the participant patient group included both those with new cancer diagnoses (where the impact of NaF-18 PET results would be on initial treatment planning) and those with suspected recurrences (in which the impact of NaF PET results would be on subsequent treatment management).

Please also note that among the 14 articles dealing with oncologic uses of NaF-18 PET mentioned in the 2009 NIH review, the following seven (summarized in this section) described case series of sufficient size to merit detailed discussion in this decision memorandum. Of the other seven articles about clinical studies of oncologic uses of NaF-18 PET, but not suitable for further review as evidence for this decision memo: three were single case reports; one was a review article; and the remaining three clinical studies (Hoegerle 1998, Hoh 1993, and Petrén-Mallmin 1998) are summarized below under 'Part III Section 8 - Public Comments'.

The 2009 NIH review summarized certain common findings from studies of NaF-18 PET and bone metastases:

"Diagnostic imaging has played a major role in the evaluation of patients with bone metastases, and this application is the focus of the majority of the recent published literature on use of 18F-fluoride PET. For detection of bone metastases in cancer patients, doses typically ranged from 8 to 12 mCi. In this dose range, excellent image quality with higher spatial resolution than conventional BS is obtained. There is evidence that 18F-fluoride PET is more sensitive and selective than conventional BS for diagnosis and detection of bone metastases … Use of low-dose CT in conjunction with 18F-fluoride PET improves sensitivity and specificity, and improves the ability to distinguish benign from malignant lesions. Because of these advantages, and advancements in cost-effectiveness, it has been suggested that 18F-fluoride PET will replace conventional bone scan for detection of bone metastases within several years. Studies presented in this review showed sensitive and specific detection of bone metastases with administration of 18F-fluoride PET at doses ranging from 7−20 mCi (261−740 MBq). Several of these studies included subjects with multiple types of cancer; studies in cohorts specific to lung, breast and prostate cancer patients are also presented. No safety issues were mentioned in any of these publications nor were any safety reports identified in a search of FDA's Adverse Event Reporting System (AERS) database."

The following seven published articles, each of which was included in the 2009 NIH review, were subsequently reviewed by CMS:

Beheshti 2008

In this prospective study of thirty-eight male patients with biopsy proven prostate cancer, NaF-18 PET-CT was compared with F-18 fluorocholine PET-CT for the detection of bony metastases. The patients' average age was 69 years. Patients were included for either increased pre-operative suspicion of metastatic prostate cancer (either high-grade cancer on biopsy or elevated PSA levels) or post-operatively with evidence of disease progression or suspicion of bone metastases based on other imaging modalities. For each patient, the interval between NaF-18 PET and F-18 fluorocholine PET-CT scan performance was less than two weeks. Patients with a history of a second cancer and patients with low-risk prostate cancers were excluded. NaF-18 PET scanning was initiated 60 min after injection of 370-550 MBq of NaF-18.

Scan images were examined by two nuclear medicine radiologists and a nuclear medicine physician who had access to clinical and previous imaging information. Lesions in the skull, distal femora, and both feet were excluded from the study. Lesions were considered benign if they were consistent with the morphologic alterations of osteoarthritis. Focal PET lesions with findings on CT consistent with metastases were considered malignant. Lesions were considered equivocal if they were not benign or malignant. A 'final' diagnosis was established by histopathological findings or by clinical or imaging follow-up studies after at least 6 months (ranging from 6 – 15 months). Fifteen equivocal lesions with no final diagnosis were eliminated from the study.

The authors found that, while there were no significant differences in sensitivity for lesions detected between the NaF-18 PET (74%) and F-18 fluorocholine PET-CT (81%) methods, F-18 fluorocholine specificity was significantly greater (99% vs. 93%, $p < 0.01$). Diagnostic accuracy was similar for NaF-18 PET and F-18 fluorocholine (85% vs. 86%). The authors also commented that, while NaF-18 PET detected more lesions per patient, it did not change patient outcomes compared with F-18 fluorocholine imaging.

Evan-Sapir 2004

In this study, scans were performed on 44 consecutive oncologic patients (20 male and 24 female; mean age, 52 +/- 17 y; range, 15–81 y). Indications for the study included: to survey for metastatic disease (as an alternative to ^{99m}Technetium (Tc) methylene diphosphonate (MDP) bone scintigraphy) (n = 21); to investigate skeletal pain for which the results of bone scintigraphy were normal (bone scintigraphy was performed 1–6 wk before the NaF-18 study) (n = 12), and to investigate bone highly suggestive of tumor involvement because of abnormal laboratory findings (e.g., elevated blood tumor markers) or unclear findings on other imaging modalities (n = 10). The final diagnosis of lesions was based on histopathology, correlation with contemporaneous diagnostic CT or MRI, or clinical follow-up of at least 6 months (mean, 10 +/- 3 mo). Increased 18F-fluoride uptake was detected at 212 sites, of which 111 were considered malignant lesions, 89 were considered benign, while the final diagnosis for lesions at 12 sites could not be determined.

On PET/CT, 94 of 111 (85%) detected lesions presented as sites of increased uptake with corresponding lytic or sclerotic changes on CT, and 16/111 lesions detected on PET/CT showed normal-appearing bone on CT, for an overall sensitivity of 110/111 (99%) for tumor detection. PET/CT was therefore misleading for only 1 detected 'metastatic' lesion, and other findings suggested a false positive diagnosis of a benign lesion. The specificity of PET/CT was significantly higher than that of PET alone (97% vs. 72%, $p < 0.001$). PET/CT identified benign abnormalities at the location exactly corresponding to the scintigraphic increased uptake for 85 of 89 (96%) benign lesions.

In a patient-based analysis, the sensitivities of PET and PET/CT for malignancy were 88% and 100%, respectively ($p < 0.05$) and the specificities were 56% and 88%, respectively (not statistically significant). Among the 12 patients referred for NaF-18 PET assessment because of bone pain despite negative findings on ^{99m}Tc-MDP bone scintigraphy, NaF-18 PET/CT suggested malignant bone involvement in all 4 patients who had proven skeletal metastases, potentially benign causes of pain in 4 of 7 other patients with no evidence of metastatic disease, and in one patient who had a soft-tissue tumor mass invading a sacral foramen. Results indicate that NaF-18 PET/CT is both sensitive and specific for the detection of lytic and sclerotic malignant lesions, and may assist in identifying a potential cause for bone pain in oncologic patients. The author concluded that, for most lesions, the anatomic data provided by the low-dose CT of the PET/CT study obviates the performance of full-dose diagnostic CT for correlation purposes.

Hetzel et al., 2003

This study prospectively compared NaF-18 PET with SPECT and planar bone scan (BS) in detecting of metastases from small- and non-small-cell lung cancers to the vertebral column. Diagnostic performance of each modality was assessed in a group of 103 patients, using receiver operating characteristic (ROC) curve analysis. The median age of the 72 male and 31 female patients was 62 years, with ages ranging from 38 to 81 years. A history of extrapulmonary cancer, pregnancy and patient age less than 18 years were exclusion criteria. NaF-18 PET scanning was initiated from 75 to 180 minutes after injection of 261-740 (mean, 541) MBq of NaF-18. Patients were defined to have no bone metastasis if BS, SPECT, NaF-18 PET, and MRI were all negative. The nature of indeterminate lesions on BS was resolved due to negative findings at autopsy (in one patient) and lack of clinical progression (in the other).

The authors found that about 32% of patients had bone metastases to the vertebral column. The areas under the ROC curve for each modality in this patient population were 0.771 for BS, 0.875 for SPECT, and 0.989 for NaF-18 PET ($p < 0.05$). Compared with NaF-18 PET, the extent of metastatic bone disease was underestimated in 23 patients with BS, and in 16 patients with SPECT. Clinical management was changed in 10/103 (9.7%) of NaF -18 PET patients. The authors concluded that routine NaF-18 PET assessment results improve the therapeutic strategy because of more sensitive detection of vertebral metastases that otherwise would have been missed.

Schirrmeister et al., 1999A

This prospective study examined the accuracy of NaF-18 PET, compared with bone scintigraphy using ^{99m}Tc-MDP, for detection of bone metastases from breast cancers. 34 patients with breast cancer, ranging in age from 37-75 years with a mean age of 52 years included six patients with previously known bone metastases and 28 with suspected metastatic bone involvement due to bone pain. PET scans were initiated one hour after injections of 370 MBq of NaF, and BS and NaF-18 PET images were separately interpreted by two separate pairs of experienced nuclear medicine physicians. The degree of likelihood of a metastatic lesion in bone was rated on a consensus five-point scale. In patients with known metastases, both NaF-18 PET and BS correctly staged all six patients, although NaF-18 PET detected additional, previously unknown metastases in five patients.

In 28 patients with suspected bone metastases, NaF-18 PET correctly diagnosed bone metastases in eleven patients, and no bone involvement in 16 patients. In one patient with degenerative bone changes, NaF-18 PET was considered equivocal. No bone metastases were missed with NaF-18 PET. In contrast, BS identified only five patients correctly with bone metastases, and disease status was considered equivocal in seven patients, four of whom had bone metastases. From BS findings, eleven patients were correctly considered negative for bone metastases, while three patients with metastatic bone involvement were incorrectly found to be negative. NaF-18 PET revealed the full extent of bone metastases in eleven patients of the 28 with previously unknown metastases, while BS revealed the full extent bone metastases in four of those 28 patients. In all patients, 168 osseous lesions (96 correctly called benign, 64 correctly considered to be metastases, and eight lesions equivocal) were revealed by NaF-18 PET, while BS revealed 89 lesions, of which 69 were judged correct (39 benign, 29 metastatic). All lesions detected with BS were also visible on PET scans. ROC curve analysis for patients correctly diagnosed showed that the area under the ROC curve was 1.00 for NaF-18 PET and 0.82 for BS ($p < 0.5$).

The study also examined changes in patient management from NaF-18 PET compared with BS findings, and found that clinical management was changed in 4/34 patients (12%). In two other patients, BS was falsely positive, but NaF-18 PET negative findings for bone metastases were included in treatment planning prior to initiation of therapy. The authors concluded that NaF-18 PET is superior to BS for diagnostic accuracy and influenced or changed patient management in 6/34 patients (18%) with known or suspected bone metastases from breast cancer.

Schirrmeister et al., 1999B

In this study, 44 individuals with proven prostate, lung or thyroid cancer of stages III or IV were examined with planar radionuclide bone scans (RNB) using ^{99m}Tc MDP and with NaF-18 PET. Patients who were pregnant or who had known disseminated metastatic disease were excluded. A panel of reference methods, including MRI of the spine, ^{131}I scintigraphy, conventional radiography and spiral CT, was used as the gold standard. On a lesion by lesion basis, NaF-18 PET showed more metastases than RNB in patients with prostate (67 lesions (NaF-18 PET) vs. 33 (RNB)), and more metastases in patients with lung or thyroid (29 lesions vs. 13) cancer. NaF-18 PET detected a total of 135 metastatic lesions in the spine, compared to RNB detection of 55 spinal lesions. All lesions detected with RNB were also detected with NaF-18 PET. Area under the ROC curve was 0.99 for NaF-18 PET and 0.64 for RNB. The authors concluded that bone imaging with NaF-18 PET is more sensitive than RNB imaging in the detection of malignant bony lesions, and that the sensitivity of NaF-18 PET for such lesions is not limited by anatomic location. The authors favored further comparison studies of NaF-18 PET scanning with bone scintigraphy.

Schirrmeister et al., 2001A
In this prospective study, NaF-18 PET diagnostic performance and implications for clinical management were compared with those of planar bone scans (BS) and SPECT imaging in a group of 53 patients with newly diagnosed lung cancer (42 men, 11 women; age range, 43–78 y; median age, 63 y; mean age, 63.2 y). Exclusion criteria included: history of extrapulmonary cancer, known metastatic bone disease, NSCLC lower than stage III, pregnancy, or an age of 18 y. MRI and all available imaging methods, as well as the clinical course, were used as reference methods. The authors indicated that "… Lesions not detectable on planar BS but showing the typical pattern of BM from SPECT or 18F PET and from MRI were defined as metastases. Lesions that were unclear at MRI but negative according to each scintigraphic method were assessed with FDG PET and with spiral CT. In the case of negative FDG PET and spiral CT results, these patients underwent curative surgery and the results of MRI were assessed by autopsy (1 patient) or evaluated by the clinical course (1 patient)."

BS with and without SPECT and 18F PET were compared using a receiver operating characteristic (ROC) curve analysis. Twelve of 53 (23%) of patients scanned had bone metastases. BS produced 6 false-negatives, SPECT produced 1 false-negative, and NaF-18 produced no false-negatives. The area under the ROC curve was 0.779 for BS, 0.944 for SPECT, and 0.993 for NaF-18 PET. Based on results of SPECT or NaF-18 PET imaging, clinical management was changed in 5/53 patients scanned (9%) or 6/53 patients scanned (11%), respectively. The authors concluded that NaF-18 PET is the most accurate whole-body imaging modality for screening for bone metastases and in some cases may alter clinical management.

Schirrmeister et al., 2001B
This article was based on a study of imaging results in a case series of 35 patients with thyroid cancer who had previously undergone thyroidectomy. The study population included 9 males and 26 females with mean age of 62 years and age range of 36-89 years. Patients were included in the study if one of the following criteria were present: known distant metastases from differentiated (papillary or follicular) thyroid carcinoma; elevated serum thyroglobulin; or newly diagnosed bone pain. Bone scintigraphy (BS) and NaF PET were performed in 21/35 patients who reported bone pain and/or who had elevated thyroglobulin. In 14/35 patients, BS and NaF PET were performed to define the extent of bone metastases (BM) and for guidance of therapy. All patients underwent NaF-18 PET, x-ray, planar bone scintigraphy (BS) using ^{99m}TC-MDP, lung computed tomography and whole body ^{131}I scintigraphy (WBI); the study's results suggest that some patients also underwent FDG PET imaging. Imaging studies were evaluated by two nuclear medicine physicians who were blinded to results of other imaging modalities.

NaF PET was used to evaluate the degree of reactive bone mineralization. Lesions were considered bone metastases (BM) if they appeared as cold lesions, or as hot spots not located at articulations, and if they could be distinguished by lack of the typical liner tracer uptake of end plate fractures. Clinical follow-up ranged from 1.5 – 4 years. NaF PET imaging identified 21 previously unknown metastases, with 13/21 showing lot sclerotic activity, while 8/21 metastases showed focally increased tracer accumulation interpreted as osteosclerotic activity. The sensitivity of the combination of BS and WBI was as high as that obtained with NaF-18 PET and MRI, which were used as the primary reference methods. The authors concluded that BS in combination with WBI was highly accurate for detecting BM from differentiated thyroid carcinoma using NaF-18 PET with MRI as the reference comparison method.

3. Internal technology assessment

Literature Search
CMS performed a separate literature search utilizing PubMed for randomized controlled trials (RCTs), systematic reviews, and series studies evaluating the technology used for the diagnosis of bone metastasis. The literature search was limited to studies of human patients, and to articles in English. One additional article about a relevant clinical trial was found beyond those summarized above.

Evan-Sapir 2006
In this prospective study comparing NaF-18 PET and bone scintigraphy using ^{99m}Tc-MDP, 44 patients with high-risk prostate cancer were imaged with both methods on the same day. The 44 male patients had a mean age of 71.6 years. 25/44 patients were newly diagnosed, with either Gleason scores of 8 or more, or with PSA levels greater than or equal to 20 ng/mL, or with nonspecific sclerotic lesions on CT. The other 19/44 patients were referred for evaluation of suspected recurrence or progression of disease. Following BS, NaF-18 PET/CT scanning was initiated 60-90 minutes after intravenous injection of 296-444 MBq of F-18 NaF-18.

Of the 44 study patients, 23 (52%) had bone metastases based on definitive PET/CT findings, biopsy, and imaging follow-up. In 20/23 patients, PET/CT clearly identified malignant bone involvement with characteristic osteoblastic lesions by CT. In three of 23 patients with 'equivocal lesions, increased focal uptake of NaF-18 PET occurred in areas in which CT images were considered normal. However, follow-up and/or biopsy confirmed the malignancy of these lesions. The patients with no evidence of bone metastases on NaF-18 PET/CT had no clinical or imaging evidence of metastatic disease for at least the six month follow-up period. The following table shows the comparison (on a per-patient basis) of planar BS vs. NaF-18 PET/CT.

	Sensitivity	Specificity	PPV	NPV
Method				

	57%	57%	59%	55%
Planar BS				
	100%	100%	100%	100%
NaF-18 PET/CT				

Among the patients with newly diagnosed disease, NaF-18 PET/CT accurately identified or suggested the presence of metastatic bone spread in eleven patients, and excluded bone metastases in 14 patients. In five of the eleven patients with previously unknown bone metastases, patient management was altered. Among the 12 patients with suspected disease recurrence or progression, NaF-18 PET/CT was associated with a change in therapy in four patients. The authors concluded that, compared with BS, NaF-18 PET/CT is highly sensitive and specific for detecting bone metastases in patients with high-risk prostate cancer, and has the potential to change patient management.

4. MEDCAC

CMS did not convene the MEDCAC for this reconsideration.

5. Evidence based Guidelines

We expect to receive evidence-based guidelines relevant to this proposed decision.

6. Professional Society Position Statements

We expect to receive professional society position statements on this proposed decision.

7. Expert Opinion

We expect to receive expert opinion on this proposed decision.

8. Public Comments

A number of individuals submitted comments about this coverage topic. All favored CMS coverage of NaF-18 PET as an alternative imaging modality to detect bony metastases.

Speaking to the use of this imaging method, a number of commenters cited the relative technical advantages of NaF-18 PET scanning, the clarity of the images produced, and the method's ability to demonstrate bone turnover from metastatic lesions, rather than being tied to glucose avidity which was felt to potentially limit F-18 FDG PET sensitivity in bone. A number of commenters also indicated favorably their current experience with NaF-18 PET scanning, and cited the relative availability of sources of F-18 PET/CT resources.

Finally, many comments included concerns that, given the expected shortage of 99mTc for bone scans, NaF-18 PET would soon become 'necessary' in view of the absence of other options.

Several additional citations of articles with clinical trial evidence relevant to this decision memo were offered for CMS review. Several commenters also mentioned the NIH review and evidence summary of uses of NaF PET.

Two of these citations (Damle 2007; Kawaguchi 2008) were of abstracts of clinical studies. These two citations are listed separately as "Abstracts" in the list of references at end of this decision memo. CMS generally does not include results of abstracts of clinical studies in coverage decisions, due to the absence of sufficiently detailed data for CMS review and study.

Other articles cited by public commenters included the following, which, despite their individual value for certain purposes, are not considered sufficiently relevant to the topic and purpose of this decision memo to be included among the articles cited as "Evidence" in the preceding sections.

Bridges 2007
This article includes a helpful historical and technical review of NaF-18 PET imaging, including a number of case examples of the use of this modality in various clinical situations.

CMS response: While furnishing interesting background, this article does not present the results of a clinical study or meta-analysis for review.

Hoegerle 1998

In this study of a consecutive case series of 60 patients (23 women and 37 men with an average age of 51 years, ranging from 13 – 76 years), 30 patients underwent FDG PET imaging only; and 30 underwent combined FDG PET and NaF-18 PET imaging. The study examined the feasibility of such combined imaging and the relative value of its assessment of metastatic lesions in bone, compared with FDG-PET imaging alone. In the group with combined FDG and NaF-18 PET imaging, both radiopharmaceuticals were injected in a peripheral vein, and after a 90 minute uptake period, scanning was initiated. Interpretations of all PET images were done in a blinded manner by two observers, and results reflected the consensus of observers. Results were later correlated with those of other imaging studies, including CT, MRI, plain radiography, and bone scintigraphy). Biopsy was not performed. In the study group with combined FDG and NaF-18 PET imaging, 73 lesions were detected; in the control group with FDG PET alone, 69 lesions were detected. The authors commented that the combined FDG and NaF-18 PET images allowed enhanced distinction of soft tissue lesions.

CMS response: The value of this interesting study of a combined radiotracer technique for the present decision memo is considered of limited relevance for this decision memo, because the technique of NaF-18 PET imaging for bone metastases was not separately addressed and evaluated.

Hoh 1993

In this study, whole-body NaF-18 PET images and CT images of the entire skeletal systems of 19 patients with known malignant and benign bony lesions were compared with similar images from 19 normal volunteers. The 19 patients with bony images were from 24 – 87 years of age. 13/19 patients had biopsy proven malignant bone tumors (both primary and metastatic from breast, bladder, lung, melanoma, osteosarcomas, and one from a soft tissue sarcoma), 5 had benign bone lesions (such as osteoporotic compression fractures, degenerative disk disease, and bone cyst), and 1 patient with colorectal cancer had no bone lesions. Scans were initiated 60 minutes after intravenous injection of F-18 NaF-18. Difference techniques (tomographic vs. coronal) demonstrated varying image quality. The authors concluded that NaF-18 PET imaging produced high-quality tomographic images for clinical use.

CMS response: This interesting early study, which focused on technical enhancements for improving NaF-18 PET imaging and supports the feasibility of detection of bony metastases from several types of primary malignant tumors, is not a comparative imaging study of NaF-18 PET relevant for this decision memorandum.

Iagaru 2009

This prospective pilot study of 14 patients with a variety of proven malignancies evaluated the performance of a combined NaF-18-[F-18] FDG 'cocktail' PET/CT technique for staging malignancies, including those which are not glucose-avid. The patients, eleven men and three females, averaged 50 years of age, ranging from 19–75 years of age. Each patient underwent three PET/CT scans (i.e., NaF PET, FDG PET, and then the combined cocktail NaF/FDG PET) within a two-week interval. According to the authors, " … In six patients, the skeletal disease was more extensive on the 18F PET/CT scan than on the 18F-FDG PET/CT scan, whereas in another patient 18F PET/CT showed osseous metastases and 18F-FDG PET/CT findings were negative. The remaining seven patients had no osseous metastases identified on the 18F PET/CT or the 18F-FDG PET/CT scans." In conclusion, the authors suggested that "... combined [F-18](NaF-18)/FDG scan yielded results for bone radiotracer uptake comparable to those of NaF-18 PET performed separately", and suggested that this combined technique might improve patient care and reduce health care costs.

CMS response: As a pilot project evaluating a new technique, this small, uncontrolled feasibility study yielded no evidence about outcome improvement or treatment decision impact of NaF-18 PET imaging itself.

Petrén-Mallmin 1998

This study examined the correlation of NaF-18 PET with CT scan in 5 patients with multiple known skeletal metastases from breast cancer. Study participants included 5 women who were from 50-70 years of age, with histologically proven breast cancer and known skeletal metastases. In several cases, the NaF-18 PET and CT scans occurred some time following treatment; in two other cases, a patient had been recently diagnosed and treatment had not yet begun, and in the other, chemotherapy was ongoing at the time of the NaF-18 PET and CT scans, which were performed in all cases from zero to nine days apart. PET scans were performed after injection of 200-400 MBq of NaF-18, and scanning was initiated and continued for the next 50 minutes. Using manual registration and simultaneous comparison of PET and CT images, the study noted that "… areas of abnormal high accumulation of F-18 correlated well with the pathological appearance on CT". A few areas of CT abnormality, lytic lesions of 0.3 cm in size or smaller were invisible on PET scan. Areas of presumed 'normal' bone demonstrated 5-10 times less NaF-18 uptake than focal CT lesions. The authors concluded that "… PET with F-18 fluoride demonstrates very high uptake in lytic and sclerotic breast cancer metastases."

CMS response: Although this result supports the use of NaF-18 PET for detecting bone metastases, it is based on a very small (n= 5) case series limited to patients with known advanced metastatic involvement of the skeleton, and was not judged to have sufficient methodologic rigor for further review in the Evidence section above.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Act.

In addition to § 1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:

(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(1)(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]
. . .
Section 1142 of the Act describes the authority of the AHRQ.

Under the authority of section 1862(a)(1)(E) of the Act, CMS may cover under coverage with evidence development/coverage with study participation (CED/CSP) certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A), and where additional data gathered in the context of clinical care would further clarify the impact of these items or services on the health of Medicare beneficiaries. CMS has described CED/CSP is greater detail in a guidance document available at https://www.cms.hhs.gov/ncpc_view_document.asp?id=8. See also section 310 Medicare NCD Manual. CED/CSP allows CMS to provide coverage based on a determination that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise. Under section 1142 of the Act, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically. In addition, evaluations of the comparative effects, health and functional capacity; alternative services and procedures utilized in preventing, diagnosing, treating, and clinically managing diseases, disorders, and other health conditions may be conducted.

As a general matter, CED/CSP is to be used in rare instances. For some items or services, CMS may determine that the evidence is very preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A) of the Act, but, if the following criteria are met, CED/CSP might be appropriate:

a. The evidence includes assurance of basic safety;
b. The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
c. There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future NCD that would focus on whether the item or service should be covered by Medicare under 1862(a)(1)(A) of the Act. Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

The clinical studies for which it will provide coverage must answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the NaF-18 PET study is needed to inform the antitumor treatment strategy, does the addition of NaF-18 PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the standards and address the above-listed research questions identified by CMS and AHRQ.

Based on the legal framework set forth above, this section presents the agency’s evaluation of the evidence considered and conclusions reached for the assessment questions posed above. As previously noted, PET using NaF-19 to identify bone metastasis of cancer is a diagnostic test.

The Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary’s specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of an NaF-18 PET imaging test for cancer metastasis to bone in order to assist in initial treatment planning and in identification of symptomatic bone metastases in the anticancer management of patients who are known to have cancer based on clinical findings and preliminary diagnostic testing.

We considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. We believe that evidence of improved health outcomes is more persuasive than evidence of test characteristics.

In evaluating diagnostic tests, Mol and colleagues (2003) reported: "Whether or not patients are better off from undergoing a diagnostic test will depend on how test information is used to guide subsequent decisions on starting, stopping, or modifying treatment. Consequently, the practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes." When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

As a diagnostic test, NaF-18 PET would not be expected to directly change health outcomes, i.e. there is no evidence that administration of NaF-18 is, in and of itself, therapeutic. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available management alternatives.

Questions

1. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully alter the recommended treatment strategy for beneficiaries who have cancer?

Based on published clinical studies, and on several oncology treatment guidelines, the use of NaF-18 PET for detection of bone metastases from cancer is advocated by some stakeholders for treatment planning. Studies of NaF-18 PET show high levels of sensitivity for metastatic bone lesions (Evan-Sapir 2004, Hetzel 2003, Schirrmeister 1999A, 2001A and 2001B), in some studies exceeding that of ^{99m}Tc scans. An advantage of NaF-18 PET is its ability to detect metastatic lesions in many areas of the bony skeleton in a single scan. However, false positive results due to the potential for detecting other, non-malignant lesions of bone were mentioned in several studies.

In addition, results of NaF-18 PET were found to change patient treatment in several cancers (Schirrmeister 1999A and 2001A,) in which NaF-18 PET was associated with altered patient management in 10-17% of patients. The authors also suggested that there was little difference between the impacts of NaF-18 PET and SPECT studies on treatment decisions. This was confirmed by the findings of the Hetzel 2003 study, in which results of NaF-18 PET scanning changed treatment strategy in about 10/103 lung cancer patients (9.7%), in contrast to 8/103 patients (7.8%) whose SPECT results changed treatment strategies. One other study (Evan-Sapir 2006) mentioned that NaF-18 PET did affect patient management in nine of 44 (20%) patients with high-risk prostate cancer. However, no mention of patient outcomes was included in any of these three articles.

In summary we believe that there is inconsistent evidence that the results of NaF-18 PET scans are used to alter recommended treatment strategy. We realize that the usefulness of NaF-18 PET imaging in this regard may be affected by the local availability of alternatives for the imaging of cancer metastases to bone.

2. Is the evidence adequate to conclude that the results of a NaF-18 PET scan for the identification of cancer metastasis to bone will meaningfully improve patient centered health outcomes for beneficiaries who have cancer?

Published evidence of any impact of NaF-18 PET scanning on patient centered health outcomes is very limited. None of the studies cited above examined effects of NaF-18 PET detection of bone metastases and patient survival or other outcomes. However, clinical trials currently in progress might provide further evidence of such impact. Rare clinical trials about the effects of NaF-18 PET on outcomes were noted during a search on June 30, 2009 of www.clinicaltrials.gov, using the search terms "F-18 Fluoride". Three clinical trials are currently recruiting participants to study oncologic uses of NaF-18 PET for detecting metastases.

Previous studies have examined the effects of more aggressive imaging strategies on outcomes in patients with early breast cancer. An article reviewing clinical studies of the role of bone scans for follow-up in breast cancer patients (Hayes 2007) indicates that intensive surveillance with bone scans for detection of recurrence in patients with early breast cancer does not improve mortality significantly compared with usual clinical follow-up. Such findings, corroborated by others such as that of the American Society of Clinical Oncology in 2006 (Khatcheressian 2006), are based on studies, such as those summarized in a Cochrane review (Rojas 2005) that showed

"… a regular physical and yearly mammogram are as effective as more intense methods of examination in detecting recurrent breast cancer."

CMS did not find published evidence that the above findings are generalizable to other types of metastatic cancer.

CMS found no conclusive evidence of improved patient oriented health outcomes related to NaF-18 PET studies for routine follow-up or monitoring of suspected bone metastases, except for the diagnosis of bone metastases in patients with symptomatic evidence of bone pain and with no other imaging findings of bone metastasis.

In the absence of published clinical studies of outcomes attributable to NaF-18 PET findings in such patients, CMS does not believe there is sufficient evidence to support coverage under § 1862(a)(1)(A).

Coverage under §1862(a)(1)(E)
As we noted above, we found limited evidence demonstrating that NaF-18 PET imaging for cancer metastases to bone affects physician decision making or leads to improved health outcomes in patients who have cancer. Though promising, the evidence of clinical benefit is not yet conclusive and is not generalizable to the Medicare patient population.

Rather, CMS believes that additional evidence would be necessary to establish actual clinical benefit. CMS finds the use of NaF-18 PET promising but not complete for guiding treatment strategy. We do believe that NaF-18 PET for the identification of bone metastasis of cancer is promising and support further research under §1862(a)(1)(E) and our CED policy.

As we have said in section V(B) of a previously published guidance document (https://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8),

"Coverage with study participation (CSP) will allow coverage of certain items or services for which the evidence is not adequate to support coverage under section 1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. In the past, this level of evidence would have prompted non-coverage decisions.

"CSP allows CMS to determine that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise. If CMS decides that there is limited existing evidence to support a decision to cover the item or service under review and more evidence is needed for CMS to determine whether that item or service meets the evidentiary standards for reasonable and necessary, then the item or service is found to not be reasonable and necessary for Medicare coverage under section 1862(a)(1)(A). CMS may then consider whether coverage of the item or service is reasonable and necessary for Medicare coverage under section 1862(a)(1)(E)4 of the Act."

The guidance document further notes:
"When the evidence is inadequate to determine that the item or service is reasonable and necessary under section 1862(a)(1)(A), Medicare coverage may be extended to patients enrolled in a clinical research study."

Accordingly, CMS proposes coverage for NaF-18 PET for either initial treatment planning or for detection of bone metastasis in symptomatic cancer patients following initial treatment, based on participation in clinical studies which are designed and conducted to collect clinical evidence of effects of NaF-18 PET results on outcomes such as improved survival, improved quality of life, and more appropriate referral to palliative care. Hence, we believe that such uses should generally be covered only under coverage with study participation (CSP).

Under the authority of §1862(a)(1)(E), coverage with evidence development/coverage with study participation (CED/CSP) will allow Medicare to cover certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CSP allows CMS to determine that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring and clinical expertise. Under section 1142, research may be conducted on the outcomes, effectiveness and appropriateness of health care services and procedures to identify the manner in which diseases, disorders and other health conditions can be prevented, diagnosed, treated and managed clinically.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under §1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

Ideally, this study would be designed to collect additional information at the time of the scan to assist in patient management. This study would examine valid, measurable outcomes when possible and avoid measuring intermediate outcomes. Changes in management that avoid unnecessary biopsy, invasive surgery or dangerous chemotherapeutic agents would be beneficial for patients. Outcomes that show significant changes in management with the use of NaF-18 PET scans would improve the evidence in this area.

The outcomes of greatest interest are discrete events that are readily identified. These include

- surgical procedures, including biopsies,
- anticancer chemotherapy,
- radiotherapy,
- hospitalization and
- mortality.

We believe that prospective clinical studies are required to assure that any differences in outcomes are confidently attributable to the additional information provided by NaF-18 PET rather than to bias or other factors. Furthermore, enrolled subjects must adequately represent the Medicare beneficiary population. If these or other studies produce sufficient evidence for us to confidently conclude that such uses of NaF-18 PET that are proposed for coverage under §1862(a)(1)(E) may be covered under §1862(a)(1)(A), we may reconsider this NCD in the future.

We therefore propose that NaF-18 PET to guide decisions on the initial antitumor treatment strategy and guide decisions on subsequent treatment strategies is reasonable and necessary only under §1862(a)(1)(E) Coverage with Evidence Development (CED), specifically Coverage with Study Participation (CSP).

We have consulted with AHRQ which has agreed that the study questions and requirements outlined above are consistent with section §1142 of the Act.

We remind the reader that this review is in the context of a patient who has a known diagnosis of a solid tumor and in whom his treating physician is still actively managing the treatment of the solid tumor. We are not considering the use of PET NaF-18 as a screening test rather than as a diagnostic test.

X. Proposed Conclusion

CMS on June 4, 2009 opened a reconsideration of Section 220.6 of the National Coverage Determinations Manual to review evidence on the use of NaF-18 (sodium fluoride-18) imaging (NaF-18 PET) to identify bone metastasis of cancer. CMS proposes that the evidence is not sufficient to determine that the results of NaF-18 PET imaging to identify bone metastases improve health outcomes of beneficiaries with cancer. Therefore we propose that this use is not reasonable and necessary under §1862(a)(1)(A) of the Act.

However, CMS proposes that the available evidence is sufficient to determine that NaF-18 PET imaging, to identify bone metastasis of cancer to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment is reasonable and necessary under §1862(a)(1)(E) through Coverage with Evidence Development (CED).

Therefore, we propose to cover NaF-18 PET imaging when the beneficiary's treating physician determines that the NaF-18 PET study is needed to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment, and when the beneficiary is enrolled in, and the NaF-18 PET provider is participating in, the following type of prospective clinical study:

An NaF-18 PET clinical study that is designed to collect additional information at the time of the scan to assist in initial treatment planning and in identification of symptomatic bone metastases. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The clinical studies for which it will provide coverage must answer one or more of the following questions:

Prospectively, in Medicare beneficiaries whose treating physician determines that the NaF-18 PET study is needed to inform the antitumor treatment strategy, does the addition of NaF-18 PET imaging lead to:

- A change in the likelihood of appropriate referrals for palliative care;
- Improved quality of life; or
- Improved survival?

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

We are soliciting public comments on this proposed decision pursuant to §1862(l) of the Act.

Appendix A

General Methodological Principles of Study Design

(Section VI of the Proposed Decision Memorandum)

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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